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Design, Synthesis, In Silico Studies and In Vitro Anticancer Activity of 3-(4-Methoxyphenyl)azetidine Derivatives

D. R. Parmar, R. H. Rayani, A. G. Vala, R.V. Kusurkar, R.K. Manvar, S.N. Talukdar, Preeti, **V. Zunjar,** S. Battula, J Y. Soni

Abstract

A series of 3-(4-methoxyphenyl)azetidine analogues were synthesized and screened for their in vitro anticancer activity against nine different human cancer cell lines using the cell counting kit-8 (CCK-8) assay. The synthesized molecules were characterized by 1H NMR, 13C NMR, LCMS and IR analysis. The toxicity, bioavailability and lipophilicity of all the synthesized compounds were predicted by using osiris and molinspiration model. Molecular docking study revealed that, compound 6-(3-(3-(2-aminopyridin-4-yl)-4-methoxyphenyl)azetidin-1-yl)picolinonitrile (4 A-17) and 6-(3-(4-methoxy-3-(2-methoxypyridin-4-yl)phenyl)azetidin-1-yl)picolinonitrile (4 A-19) were found to be potential inhibitor of human topoisomerase IIα. The cell viability studies exhibited promising antiproliferative activities of the novel synthesized compounds. 4 A-17 (EC50 0.03 μM) was found to be more potent than standard Doxorubicin (EC50 0.07 μM) in U251 cancer cell lines. Similarly, 4 A-19 showed considerable potency against four different cancer cell lines (HepG2, U251, A431, 786-O) with EC50 values ranging from 0.46 to 2.13 μM. These primary findings supported that molecule 4 A-17 and 4 A-19 should be subjected to further studies and lead optimization. Twenty two substituted 3-(4-methoxyphenyl)azetidines were synthesized, screened for anticancer activity against nine different cancer cell lines by CCK-8 assay. In silico study revealed 6-(3-(3-(2-aminopyridin-4-yl)-4-methoxyphenyl)azetidin-1-yl)picolinonitrile (4 A-17) and 6-(3-(4-methoxy-3-(2-methoxypyridin-4-yl)phenyl)azetidin-1-yl)picolinonitrile (4 A-19) as potential human topoisomerase IIα inhibitor. In U251 cells, 4 A-17 (EC50 0.03 μM) showed more potency than standard Doxorubicin (EC50 0.07 μM). 4 A-19 found to be more potent than Doxorubicin in HepG2. The cellular toxicity study of the novel compounds showed selectivity on cancerous cells over normal cells (HEK-293).

Keywords: azetidine; lipophilicity; molinspiration; antiproliferative; silico; osiris